REMARKS

Claims 7, 9-12 and 21-33 are currently pending in this application. Each of these claims describe inventions requiring "decreasing the mucosal damage of the intestine by administering an effective dose of HGF" that is nowhere disclosed or suggested in the prior art of record. In view of the following Remarks, Applicant respectfully requests reconsideration and timely withdrawal of the pending objections and rejections.

Examiner Interview

Applicant appreciates the courtesies extended by Examiner Borin and Supervisory Examiner Woodward during the interview of October 15, 2004. During the interview, the Applicant described the effect of HGF in a patient afflicted with various inflammatory bowel conditions. The Applicant explained that administration of HGF reduces inflammation in the intestine by reducing the gene expression of inflammatory mediators, such as TNF-α and IFN-γ. The Applicant further explained that the claimed invention is distinguishable from the cited prior art references for the same reasons the parent application was ***allowed over the same references***: the prior art references do not teach that HGF reduces inflammation in the bowel and they are directed only to *in vitro* studies and not *in vivo* studies as are the claimed inventions. Supervisory Examiner Woodward indicated that the invention ***was patentable*** over three of four references, i.e., ***not obvious*** in view of Zushi, Fukamachi and Halttunen, but requested a further review of the Ishii reference, which has now been antedated by the Rule 131 Declaration filed herewith.

Additionally, during the interview, the Examiner required clarification of the phrase "mucosal damage" as recited in independent claims 7, 21 and 26. The Applicant explained that mucosal damage is caused by inflammation of the mucosal lining of the intestinal tract, which ultimately results in the ulceration of the intestinal mucosa. Therefore, by reducing inflammation, the mucosal damage of intestinal epithelial cells would also be reduced. Moreover, the Examiner alleged that nowhere was the phrase "mucosal damage" described in the Applicant's specification. The Examiner's attention was directed to the Applicant's specification beginning at page 5, line 6 where the specification describes mucosal damage as histological lesions as well as inflammation of the bowel.

In a subsequent telephone conversation, the Examiner communicated that he had reviewed the Ishii reference and was of the opinion that the claimed invention is obvious in view of the Ishii reference. The Applicant has reviewed the Ishii reference and respectfully disagrees with the Examiner. The Ishii reference is wholly inadequate because Ishii is missing the teaching of reducing mucosal damage in a patient. In particular, nowhere does the Ishii reference teach or suggest reducing inflammation in the intestine in a patient afflicted with an inflammatory bowel condition. Again, the Ishii reference is only directed to *in vitro* studies directed to cell proliferation and not *in vivo* studies involving reducing mucosal damage of the intestine by reducing inflammation as required by the pending claims. In short, Applicant maintains that Ishii adds nothing to the prior art already of record.

Preliminary Comments

At the outset, the Applicant has been puzzled and frankly, frustrated, by how this application has been handled by the PTO. Even though the claims contain subject matter similar to parent U.S. Patent Nos. 6,319,899 and 5,972,887, the prosecution of this application has been extremely protracted and the Examiner has not set forth any new prior art or positions that have not been fully addressed in the parent patents. This application has been pending since August 2001 and has received 4 Office Actions, including two unnecessary restriction requirements, which were subsequently withdrawn by the Examiner. The Examiner issued the first restriction requirement because he failed to take into consideration the preliminary amendment filed with this application, and the second restriction requirement was completely excessive, requiring an election of species in the middle of prosecution of this application.

Moreover, all of the prior art relied upon by the Examiner throughout the four years of prosecution of this application has been previously considered and successfully distinguished in the parent U.S. patents. As discussed in more detail below, throughout the Final Office Action, the Examiner has presented arguments which were copied, ***verbatim***, from a prior office action in the parent application that are wholly inapplicable to this case. For example, the Examiner stated that the "Applicant argues that neither of the references teaches increase in the intestinal absorptive functions and intestinal mass." (Final Office Action at page 3.) Nowhere has the Applicant made such an argument. The claims in this application are **not** directed to increasing intestinal absorptive function or intestinal mass.

It is very clear this case should have been allowed a long time ago for the reasons similar to allowance of U.S. Patent Nos. 6,319,899 and 5,972,887. No new prior art has been uncovered

by the Examiner. As explained subsequently, and contrary to the Examiner's assertions on page 5 of the Final Office Action, the claims of the parent were allowed because the cell culture data could not be extrapolated to the *in vivo* processes occurring in the intestine. This prior finding by the PTO is equally applicable to the claims in this application.

The Examiner is preventing a clearly allowable invention to proceed to issue, thereby reducing the Applicant's period of exclusivity. Because the claims in this application are similar to the claims in the issued parent U.S. Patent No. 5,972,887 (indeed the Examiner has issued an obviousness-type double patenting rejection), the Examiner's actions in this case are tantamount to "questioning the validity or patentability of a U.S. Patent" in direct contravention of the statutory presumption of validity and Office policy. (*See* 35 U.S.C. § 282 and MPEP § 1701, entitled "Office Personnel Not to Express Opinion on Validity or Patentability of Patent."

Although it is completely unnecessary, in order to expedite prosecution and place this case in clear condition for allowance, Applicant files concurrently herewith a Declaration Under Rule 131 of the inventor ("Schwartz Declaration"). The Schwartz Declaration antedates and removes three of four references (i.e., Zushi, Ishii and Halttunen) relied upon by the Examiner, including the only reference (Ishii) that Supervisory Examiner Woodward indicated should be reviewed further.

Traversal of Rejections Under 35 U.S.C. § 103

The Examiner has maintained the rejections of claims 7, 9-12, and 21-33 under 35 U.S.C. § 103(a) as being "obvious over Zushi and Ishii and Fukamachi and Halttunen." (Final Office Action at page 2.) Further, the Examiner has submitted that the rejection is maintained "for the

reasons of record as applied to claims 7-12 in the first Office action on merits." (*Id.*) Applicant respectfully and strongly traverses this rejection.

First, three of the four references are not valid prior art references for the reasons discussed below. Secondly, none of these references, even if they all constituted prior art, whether taken singly or in combination, disclose or suggest each and every limitation of the claimed inventions. Thus, even if the combination of Zushi, Ishii, Fukamachi and Halttunen were proper, this combination would still fail to disclose or suggest the claimed inventions including at least the limitation requiring decreasing mucosal damage in the intestine by administering an effective dose of HGF.

The Schwartz Declaration Removes Three of Four References Relied Upon by the Examiner

The Applicant respectfully submits this rejection should be withdrawn for all of the reasons discussed in the response of January 21, 2004 and in the parent application. However, this rejection is clearly untenable in light of the Schwartz Declaration concurrently filed herewith, which establishes that Applicant's claimed invention antedates the Zushi, Ishii and Halttunen references relied on in the outstanding 35 U.S.C. § 103(a) rejection.

First, all three of these references qualify as alleged prior art only under 35 U.S.C. § 102(a) because their publication dates are less than one year prior to the September 19, 1996 effective filing date of this application. Specifically, the Zushi reference has a publication date of May 1996, the Ishii reference has a publication date of September 10, 1996, and the Halttunen has a publication date of November 1996. This application is entitled to benefit of the September 19, 1996 filing date of U.S. application Serial No. 08/932,391 because this

application is a divisional application of U.S. Application Serial No. 09/395,129, filed on September 14, 1999, now U.S. Patent No. 6,319,899, which in turn is a continuation-in-part application of U.S. Application Serial No. 08/932,391, now U.S. Patent No. 5,972,887, which claims priority to provisional application Serial No. 60/026,352, filed on September 19, 1996 (the '252 provisional application).

The '252 provisional application discloses the administration of an effective dose of HGF as a treatment for patients afflicted with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis. (*See e.g.*, '252 provisional application at page 5, lines 1-28.) Furthermore, the '252 provisional application discloses that administration of an effective dose of HGF stimulates growth and proliferation of intestinal cells *in vivo*. (*See id.*, at page 8, lines 19-22.) Thus, the '252 provisional application supports the pending claims and establishes that the Zushi, Ishii and Hultunen references qualify as prior art only under 35 U.S.C. § 102(a). Therefore, these references may be removed as prior art by filing of a Rule 131 declaration.

The references of record have been cited for the teaching that HGF stimulated the proliferation, motility and growth of intestinal cells *in vitro*. Moreover, the Examiner has rejected the claimed effective dosage range of HGF under 35 U.S.C. § 103(a) as being an allegedly obvious feature or modification of the disclosure of the cited references of record. According to MPEP 715.02:

> [w]here the differences between the claimed invention and the disclosure of the reference(s) are so small as to render the claims obvious over the reference(s), **an affidavit or declaration under 37 CFR 1.131 is required to show no more than the reference shows**. In other words, where the examiner, in rejecting a claim under 35 USC 103, has treated a claim limitation as being an obvious feature or modification of the disclosure of the reference(s) relied upon, without citation of a reference which

> teaches such a feature or modification, a 37 CFR 131 affidavit or declaration may be sufficient to overcome the rejection even if it does not show such feature or modification (emphasis added).

In accordance with MPEP § 715.02, the Schwartz Declaration establishes the prior invention of at least the same teachings as the cited references of Zushi, Ishii and Halttunen. Specifically, for example, the Schwartz Declaration and its associated evidence establish that the administration of an effective dose of HGF to a subject was shown to stimulate growth and proliferation of intestinal cells *in vivo* before May 1996, the earliest publication date of the cited references of Zushi, Ishii and Halttunen. (Schwartz Declaration, ¶8).

More specifically, in his Declaration, Dr. Schwartz attests that he is the inventor of the above-identified patent application. (¶1.) Dr. Schwartz has provided as Exhibit E to his Declaration a copy of an abstract (date redacted) he authored with the assistance of his research assistants, who were working under his direct control and supervision in his research laboratory. The abstract was submitted to the American Academy of Pediatrics Section on Surgery, but does not qualify as prior art to this application. (¶6.) The abstract describes research work done in Dr. Schwartz's laboratory, and evidences that Dr. Schwartz reduced to practice in the United States the inventions disclosed and claimed in this application before the publication dates of the three references at issue.

The experimental data and information summarized in the abstract, is contemporaneous evidence of the reduction to practice of the claimed invention, performed in the United States. (¶7.) In particular, the abstract summarizes a study designed to examine the effect of systemically administered HGF on intestinal mass and function in adult male rats. (¶8.) Specifically, following a 14 day infusion period where the rats were administered either saline,

75 μg/kg/d of HGF, 150 μg/kg/d of HGF, or 300 μg/kg/d of HGF, mucosal DNA content and protein content was analyzed in a segment of the mid small intestine for each group. (*Id.*) The results of the study demonstrated for the first time that HGF can stimulate cell proliferation of intestinal epithelial cells *in vivo*. (*Id.*)

Accordingly, Zushi, Ishii and Halttunen do not constitute prior art as shown by the Schwartz Declaration, which evidences that Applicant invented at least the same teachings of the cited references prior to the earliest publication date of the cited references to Zushi, Ishii, and Halttunen.

The Claimed Inventions Distinguish Over the Cited Prior Art

Although Zushi, Ishii and Halttunen are not valid prior art references, the claimed inventions easily distinguish over the prior art of record even if the three references are not removed. The arguments presented in the Reply to Office Action dated January 21, 2004 ("the Reply") are fully incorporated herein by reference. In response to the Applicant's arguments presented in the Reply, the Examiner alleges "the rejection is under 35 USC 103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references." (Final Office Action at page 3.) The Applicant disagrees. In the instant case, none of the art references, either singly or in combination, teaches or suggests each and every limitation of the claimed inventions. Even if the combination of Zushi, Ishii, Fukamachi and Halttunen were proper, this combination would still fail to disclose or suggest at least the limitation to decreasing mucosal damage by administering an effective dose of HGF. Therefore, since the references fail to disclose or suggest each and every

limitation of the claimed invention, the Examiner has failed to establish a *prima facie* case of obviousness.

More specifically, in the Reply, the Applicant explained the deficiencies of the cited art references of record with regard to the claimed invention. Applicant established that none of the cited references disclose or suggest administering HGF to a patient to ***decrease mucosal damage***. Instead, the references cited by the Examiner are only directed to the ***proliferation*** of intestinal epithelial cells in *in vitro* cell culture systems. In particular, Zushi et al., is directed to intestinal restitution (wound resealing), Ishii et al., is directed to intestinal cell proliferation and motility using *in vitro* systems, Fukamachi et al., is directed to stimulated gastro-intestinal epithelial growth in primary cultures, and Halltunen et al., is directed to accelerated proliferation rate of T84 cells.

The Examiner has assumed that the only primary mechanism by which HGF is effective in inflammatory bowel disease is through cellular proliferation. Again, the Examiner is reminded that the Applicant's invention is directed to decreasing intestinal ***mucosal damage***, which not only includes reducing and preventing gross and histological lesions in a patient but also reducing intestinal inflammation and inflammatory mediators in a patient. The Applicant directs the Examiner's attention to the specification at page 3, lines 18-21, which states "...administering HGF to subjects characterized as having IBD reduces the gross and histologic lesions...[and] reduces the gene expression of inflammatory mediators such as TNF-α and INF-γ in these subjects."

Next, the Examiner maintains the allegation that the *in vitro* results of the cited art references can be translated to *in vivo* effects. The Examiner argues that the combined

references "demonstrate that HGF has [a] similar proliferative effect on different cell systems each of which is an adequate model of *in vivo* conditions." (*Id.*) Again, the Applicant vigorously disagrees. The *in vitro* systems used in the Examiner's cited references are immortalized cells, grown in nonphysiological conditions, none of which have been influenced by the pathological conditions of infection or inflammation that frequently occur in patients afflicted with inflammatory bowel disease. The Examiner cites no teaching prior to Applicant's discovery that HGF reduced mucosal damage. Therefore, it is scientifically, clinically and logically inaccurate to suggest that the results of *in vitro* cell culture would lead those of ordinary skill in the art to conclude that these results would provide evidence of the benefit to the clinical disorders or diseases of the intestine that are caused by infection, inflammation, or immunological disorders. At most, the references provide an invitation to try, which is clearly recognized as not being the standard for patentability. (*See, e.g.*, MPEP § 2145(X(B).)

Next, the Examiner alleges that the "Applicant argues that neither of the references teaches increase in the intestinal absorptive functions and intestinal mass." (*Id.*) The Applicant has made no such argument. The Examiner is reminded that the Applicant's claimed invention is directed to decreasing intestinal mucosal damage in a patient afflicted with inflammatory conditions of the bowel. It appears that the Examiner is relying upon arguments presented in an Office Action related to the parent case filed in 1996 that are not applicable here.

Next, the Examiner maintains his allegation that, although the references do not expressly state the claimed HGF dosages, the concentration of dosage ranges of HGF is within the skill of the ordinary worker as a part of the process of normal optimization. (*Id.*, at pages 4-5.) Additionally, the Examiner alleges that the "Applicant did not provide any factual evidence to

demonstrate unexpected results achieved by using the claim dosage range." (*Id.*, at page 5.) Nowhere has the Applicant presented any arguments directed to unexpected results achieved by using the dosage range of the claimed invention. Again, it appears that the Examiner is relying upon arguments presented in an Office Action in the parent case filed in 1996 that are not applicable here. Nonetheless, none of the art references cited by the Examiner disclose or suggest the effective HGF dosage range of the present invention. The references cited by the Examiner only provide HGF dosage ranges applicable to *in vitro* cell culture studies. It is illogical to suggest that the dose of HGF used in *in vitro* cell culture studies could be simply extrapolated by one skilled in the art to arrive at the effective HGF dosage ranges to be administered to a patient. As discussed below, this argument was explained and successfully used to distinguish the claims of parent U.S. Patent No. 5,972,887 over the same prior art references. Accordingly, the effective HGF dose would not have been obvious to one skilled in the art as the PTO previously concluded when it issued U.S. Patent No. 5,972,887 because there was no *in vitro* model that bore any relationship to short bowel syndrome. Similarly, in this application, there is no *in vitro* model that correlates to the clinical model contemplated by the claimed inventions, i.e., reducing mucosal damage by administering an effective dose of HGF.

Next, the Examiner submits that the "Applicant argues that it is assumed by the Examiner that the only primary mechanism of action of HGF is through cellular proliferation;" concluding that "without addressing the merits of such argument, the instant claims are not drawn to any particular cellular mechanism." (*Id.*) Again, the Examiner is reminded that the pending claims are directed to decreasing intestinal mucosal damage. In patients afflicted with inflammatory bowel disease, mucosal intestinal damage generally corresponds to the degree of inflammation of

the mucosal lining of the intestine. Indeed, it is the inflammation of the mucosal lining of the intestinal tract which ultimately results in ulceration of the intestine. Therefore, the phrase "decreasing the mucosal damage of the intestine" as recited in the claims is directed to reducing inflammation as well as reducing intestinal lesions.

Finally, the Examiner alleges that "after discussing the claimed subject matter in the parent case, the applicant agreed to limit claim language to an embodiment of increasing intestinal absorptive functions and intestinal tissue mass beyond the normal adaptive response." (*Id.*) Although it was agreed to amend the claims as such, it was also agreed to limit the scope of the claims to other *in vivo* conditions such as an intestinal inflammatory process. Accordingly, the same *in vivo* conditions that were incorporated into the claims of the parent case have been incorporated into the pending claims of this application. ***The rejections of the parent application, now U.S. Patent No. 5,972,887, were withdrawn by the Examiner because the cell culture data could not be extrapolated to mucosa undergoing the process of intestinal adaptation. Similarly, the cell culture data presented in the cited references here cannot be extrapolated to the in vivo histology, pathology or the results obtained with HGF in a model of immunologically induced bowel disease of the invention. Therefore, the Applicant respectfully submits that the claims of this application patentably distinguish over the prior art relied upon by the Examiner, even if the references are considered on their merits.***

Traversal of Obviousness – Type Double Patenting Rejection

The Examiner has rejected claims 7, 9-12 and 21-33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No.

5,972,887. Applicant respectfully requests withdrawal of this rejection in view of the terminal disclaimer filed concurrently herewith.

Extension of Time

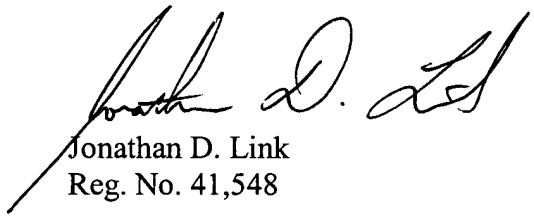
A Petition for a two (3)-month extension of time under 37 C.F.R. § 1.136(a) and accompanying fee in the amount of $ 510.00 is filed herewith extending the period for responding to the outstanding office action. Applicant believes that no further extensions of time are required other than those in the accompanying Petition. If extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. § 1.136(a). Any fees required for further extensions of time and any fees for the net addition of claims are hereby authorized to be charged to our Deposit Account No. 23-1951.

CONCLUSION

Applicant submits that a full and complete response has been made to the pending Office Action and respectfully submits that all of the stated objections and grounds for rejection have been overcome or rendered moot. Accordingly, Applicant respectfully submits that all pending claims are patentably distinct from the prior art of record and are in condition for allowance. The Examiner is thus respectfully requested to promptly pass the above application to issue.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the Applicant's undersigned representative at the number below to expedite prosecution. Prompt and favorable consideration of this Reply is respectfully requested. Applicant respectfully requests that a timely Notice of Allowance be issued for this application.

Respectfully submitted,



Jonathan D. Link
Reg. No. 41,548

Richard S. Meyer
Reg. No. 32,541

Date: **January 25, 2005**

McGuireWoods LLP
1750 Tysons Boulevard
Suite 1800
McLean, VA 22102-4215
Tel: 703-712-5116
Fax: 703-712-5279

\\COM\479359.1